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# ONE POT SYNTHESIS OF OPTICALLY ACTIVE 4-ISOXAZOLINES BY ASYMMETRIC ADDITION OF ALKYNYLZINC REAGENTS TO NITRONES FOLLOWED BY CYCLIZATION

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**Abstract** – One pot synthesis of optically active 4-isoxazolines was achieved by asymmetric addition of alkynylzinc reagents to nitrones utilizing di(*t*-butyl) (*R,R*)-tartrate as a chiral auxiliary followed by cyclization. By addition of dimethylzinc, the cyclization step was accelerated to afford the corresponding 4-isoxazolines with up to 93% ee. Furthermore, a cyclized zinc intermediate could be trapped with formaldehyde to give the corresponding 2,3,4,5-tetrasubstituted 4-isoxazoline with 85% ee.

## INTRODUCTION

Compounds bearing a 4-isoxazoline ring are versatile synthetic intermediates<sup>1</sup> and the key components of optically active nitrogen-containing substances, which have potentially high value in chemical and medicinal fields.<sup>2</sup> One of the most attractive approaches to the synthesis of 4-isoxazolines is 1,3-dipolar cycloaddition of nitrones to acetylenes, however, the method often suffered with poor regioselectivity. Alternative route to 4-isoxazolines is condensation of unsaturated ketones with hydroxylamines.<sup>1</sup> Ring-closure reaction of *N*-propargyl hydroxylamines catalyzed by zinc or palladium salt also gave 4-isoxazolines.<sup>3</sup> Furthermore, direct ring-closure reaction of zinc salt of *N*-propargyl hydroxylamines, generated in situ by addition of alkynylzinc reagents to nitrones, was reported.<sup>4</sup> However, it was mentioned that an ester or amide group was necessary in the nitrone for the promotion of the cyclization, and the cyclization took place for a simple nitrone only when an alkyne contained an acetyl group.<sup>4b</sup> Recently, we developed a catalytic asymmetric addition reaction of alkynylzinc reagents, which were prepared in situ from dimethylzinc and 1-alkynes, to nitrones by utilizing di(*t*-butyl) (*R,R*)-tartrate [(*R,R*)-DTBT] as a chiral auxiliary to afford the corresponding optically active *N*-(*R*)-( $\alpha$ -

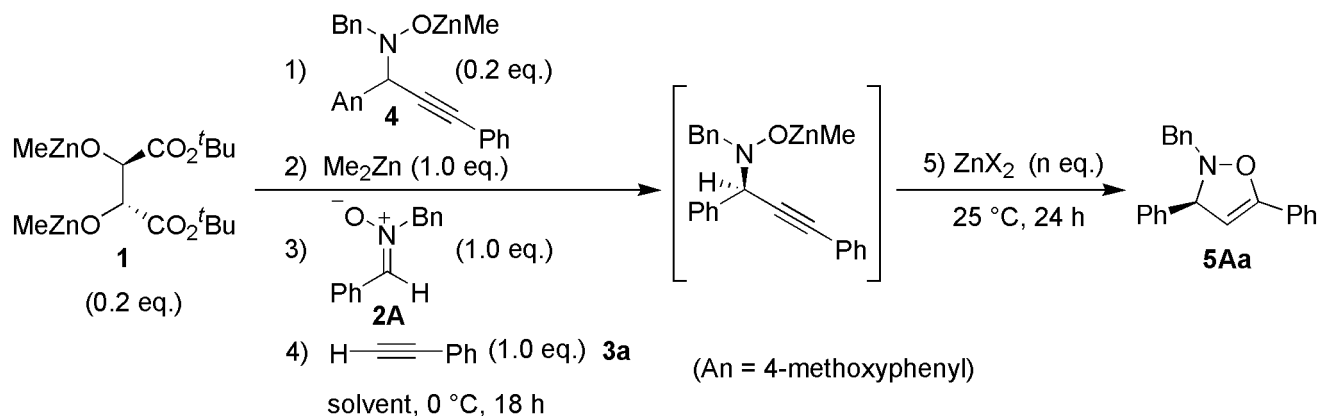
substituted)propargyl hydroxylamines. At the same time, we found an unprecedented phenomenon, enantiomeric enhancement by addition of methylzinc salt of a product-like racemic hydroxylamine as an additive.<sup>5</sup> During the course of the investigation of the enantiomeric enhancement, a part of the addition product was observed to cyclize giving the corresponding 4-isoxazoline at the later stage of the reaction. Herein, we wish to describe a tandem reaction consisting of a catalytic enantioselective nucleophilic addition of alkynylzinc reagents to nitrones followed by cyclization in the presence of a (*R,R*)-tartaric acid ester as a chiral auxiliary to give the corresponding (*S*)-4-isoxazolines with excellent enantioselectivity of up to 93% ee. Furthermore, an intermediary 4-isoxazolin-4-yl zinc species could be trapped by formaldehyde to form a new carbon-carbon bond to afford the corresponding optically active 2,3,4,5-tetrasubstituted 4-isoxazoline.

## RESULTS AND DISCUSSION

First an asymmetric addition reaction of alkynylzinc to *N*-benzyl nitrone **2A** followed by cyclization was examined (Table 1); *i.e.*, to a mixture of 0.2 molar amount of bis(methylzinc) salt of (*R,R*)-DTBT and 0.2 molar amount of methylzinc salt of racemic 4-methoxyphenyl substituted hydroxylamine **4** in toluene, equimolar amounts of dimethylzinc, nitrone **2A** and phenyl acetylene (**3a**) were successively added at 0 °C. After stirring for 18 h at 0 °C, the reaction mixture was warmed up to room temperature (25 °C) and kept for 24 h to give the cyclized product, (*S*)-2-benzyl-3,5-diphenyl-2,3-dihydroisoxazole (**5Aa**), in 51% yield and 90% ee (Entry 1).<sup>6</sup> In order to improve the cyclization step, 1.0 molar amount of zinc iodide dissolved in THF was added as a promoter after the initial addition reaction. After stirring for 24 h at room temperature, the corresponding **5Aa** was obtained with enantioselectivity of 91% ee, but only in 32% chemical yield (Entry 2). Dimethylzinc was next examined as a promoter instead of zinc iodide. To our delight, the cyclization reaction proceeded smoothly by using 1.6 molar amounts of dimethylzinc to give **5Aa** in improved 67% yield with high enantioselectivity (89% ee, Entry 3). When 3.2 molar amounts of dimethylzinc were used, the chemical yield of **5Aa** was further increased to 73% with 91% ee (Entry 4). The same reaction was also carried out in ethylbenzene, whereas the chemical yield was not satisfactory in comparison with that in toluene (Entries 4 and 5). A control experiment was carried out in the absence of methylzinc salt of racemic 4-methoxyphenyl substituted hydroxylamine **4**. The cyclized product was obtained in only 64% ee (Entry 6), which again confirmed that enantiomeric enhancement could be achieved by employing the racemic product-like additive **4**.

Asymmetric addition of several alkynylzinc reagents to other nitrones **2** followed by cyclization was performed under the optimum conditions to furnish the corresponding (*S*)-2-benzyl-4-isoxazolines **5** with high enantioselectivity (Table 2). The reaction of 2-bromophenyl substituted nitrone **2B** with phenyl

**Table 1.** Asymmetric addition of alkynylzinc reagents to the nitron **2A** followed by cyclization



Entry	$\text{ZnX}_2$	n / eq.	Solvent	Yield / %	ee / % <sup>a</sup>
1	--	0	PhMe	51	90
2	$\text{ZnI}_2^b$	1.0	PhMe	32	91
3	$\text{ZnMe}_2$	1.6	PhMe	67	89
4	$\text{ZnMe}_2$	3.2	PhMe	73	91
5	$\text{ZnMe}_2$	3.2	PhEt	60	90
6 <sup>c</sup>	$\text{ZnMe}_2$	3.2	PhMe	79	64

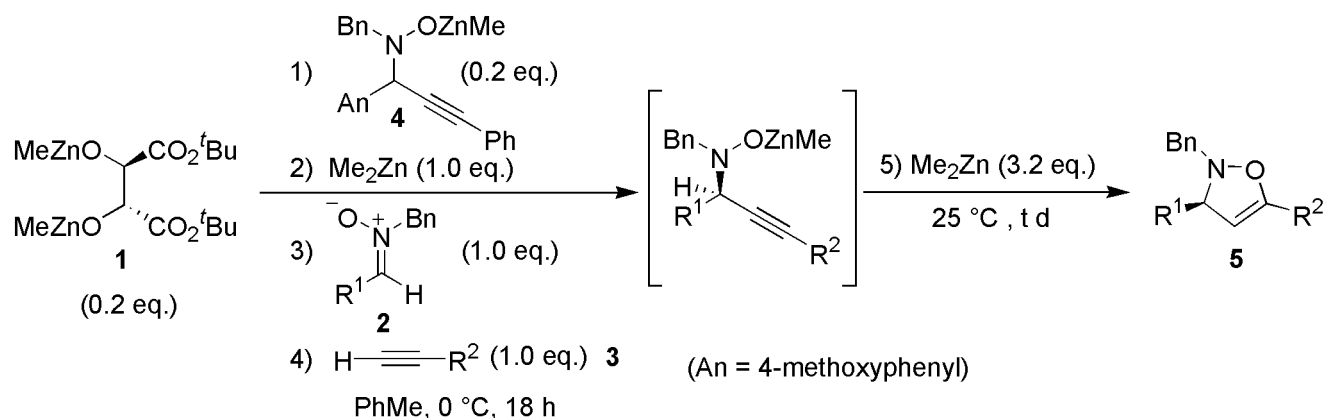
<sup>a</sup>Enantioselectivities were determined by HPLC analysis (Daicel Chiralcel OD-H). <sup>b</sup> $\text{ZnI}_2$  dissolved in THF was added into the reaction mixture. <sup>c</sup>Reaction was carried out without **4**.

acetylene (**3a**) proceeded smoothly to give the desired product **5Ba** at room temperature with 93% ee (Entry 2). 4-Bromophenyl substituted nitron **2C** also gave good enantioselectivity with 86% ee (Entry 3). Other aromatic acetylenes **3b** and **3c** reacted with **2A** to give the corresponding 4-isoxazolines **5Ab** and **5Ac** with up to 93% ee (Entries 4 and 5). Aliphatic acetylenes **3d** and **3e** afforded the corresponding 4-isoxazolines **5Ad** and **5Ae** in both good yields and enantioselectivities (Entries 6 and 7).

Finally, a cyclized zinc intermediate produced by tandem asymmetric addition/cyclization reaction was trapped with formaldehyde at room temperature to furnish (*S*)-2-benzyl-3,5-diphenyl-2,3-dihydroisoxazol-4-yl)methanol (**6**) in decent chemical yield and good chiral induction with 85% ee in the presence of a product-like additive **4** (Scheme 1).<sup>7</sup>

As described above, a catalytic asymmetric addition of alkynylzinc reagents to nitrones followed by cyclization has been developed to provide synthetically useful optically active 4-isoxazolines. By addition of a product-like substrate, the excellent enantioselectivities were realized.<sup>8</sup> Furthermore, a new carbon-carbon bond formation was achieved by the treatment of the intermediary 4-isoxazolin-4-yl zinc species with formaldehyde to afford the corresponding optically active 2,3,4,5-tetrasubstituted 4-isoxazoline.

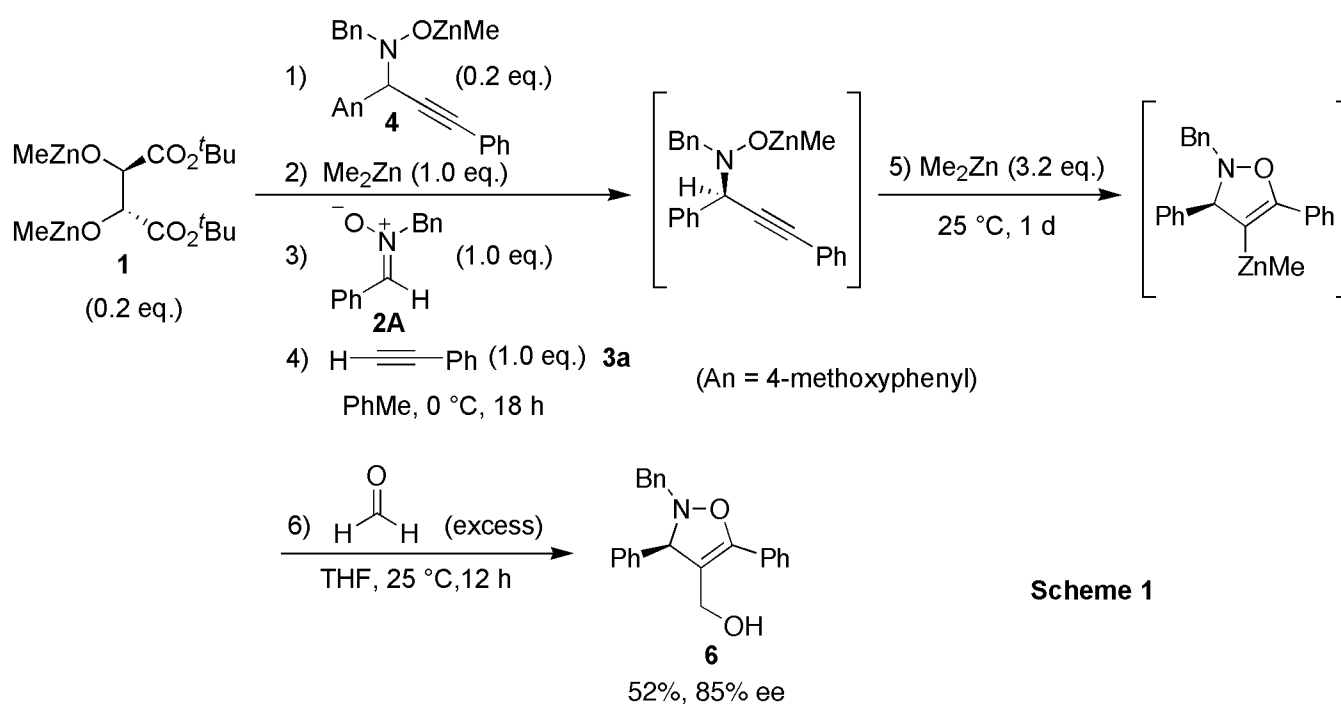
**Table 2.** Asymmetric addition of alkynylzinc reagents to nitrones **2** followed by cyclization



Entry	R <sup>1</sup>	<b>2</b>	R <sup>2</sup>	<b>3</b>	t / d	<b>5</b>	Yield / %	ee / %
1	Ph	<b>A</b>	Ph	<b>a</b>	1	<b>Aa</b>	73	91 <sup>a</sup>
2	<sup>2</sup> BrC <sub>6</sub> H <sub>4</sub>	<b>B</b>	Ph	<b>a</b>	3	<b>Ba</b>	72	93 <sup>a</sup>
3	<sup>4</sup> BrC <sub>6</sub> H <sub>4</sub>	<b>C</b>	Ph	<b>a</b>	2	<b>Ca</b>	51	86 <sup>b</sup>
4	Ph	<b>A</b>	<sup>4</sup> PenC <sub>6</sub> H <sub>4</sub>	<b>b</b>	3	<b>Ab</b>	42	93 <sup>a</sup>
5	Ph	<b>A</b>	<sup>4</sup> BrC <sub>6</sub> H <sub>4</sub>	<b>c</b>	3	<b>Ac</b>	62	85 <sup>a</sup>
6	Ph	<b>A</b>	<sup>n</sup> C <sub>4</sub> H <sub>9</sub>	<b>d</b>	3	<b>Ad</b>	70	80 <sup>a</sup>
7	Ph	<b>A</b>	<sup>n</sup> C <sub>6</sub> H <sub>13</sub>	<b>e</b>	3	<b>Ae</b>	63	85 <sup>a</sup>

<sup>a</sup>Enantioselectivity was determined by HPLC analysis (Daicel Chiralcel OD-H).

<sup>b</sup>Enantioselectivity was determined by HPLC analysis (Daicel Chiralcel IA).



**Scheme 1**

## EXPERIMENTAL

All of the melting points were determined by a micro melting apparatus (Yanagimoto-Seisakusho) and uncorrected. The  $^1\text{H}$  NMR spectra were recorded on a JEOL Lambda 400 and JEOL Lambda 300 spectrometers. The chemical shifts were determined in the  $\delta$ -scale relative to tetramethylsilane ( $\delta = 0$ ) as an internal standard. The IR spectra were measured by JASCO FT/IR-230 spectrometer. The specific optical rotations were recorded on JASCO DIP-370 spectrometer. THF was freshly distilled from sodium diphenylketyl. All other solvents were distilled and stored over drying agents. Flash column chromatography and thin-layer chromatography (TLC) were performed on Cica-Merck's silica gel 60 (No. 9385-5B) and Merck's silica gel 60 PF<sub>254</sub> (Art. 107749), respectively.

**Representative Procedure for Tandem Asymmetric Addition/Cyclization with Nitron 2A (Table 1, Entry 4):** To a toluene (3 mL) solution of (*R,R*)-DTBT (26 mg, 0.1 mmol) was added dimethylzinc (0.8 mL of 1.0 M solution in hexane, 0.8 mmol) at 0 °C under an argon atmosphere, and the mixture was stirred for 10 min. To the solution, a toluene (3 mL) solution of racemic *N*-benzyl-*N*-[1-(4-methoxyphenyl)-3-phenylprop-2-ynyl]hydroxylamine (34 mg, 0.1 mmol) was added, and the mixture was stirred for 10 min. A toluene (3 mL) solution of nitron **2A** (106 mg, 0.5 mmol) and a toluene (3 mL) solution of phenylacetylene (**3a**) (51 mg, 0.5 mmol) were added to the resulting solution successively. The reaction mixture was kept for 18 h at 0 °C. Then additional dimethylzinc (1.6 mL of 1.0 M solution in hexane, 1.6 mmol) was further added to the reaction mixture at 0 °C. The resulting solution was warmed up to 25 °C and stirred for 1 d, followed by addition of a saturated aq.  $\text{NH}_4\text{Cl}$  solution to quench the reaction. After filtration of the precipitate, the filtrate was extracted with AcOEt. The combined extracts were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and condensed under reduced pressure. The residue was separated by TLC on  $\text{SiO}_2$  (hexane/AcOEt = 3/1) to isolate the corresponding **5Aa** (114 mg, 73%, 91% ee).

**(*S*)-2-Benzyl-3,5-diphenyl-2,3-dihydroisoxazole (5Aa):**<sup>3b</sup> A solid. Mp 133–134 °C (from EtOH).  $[\alpha]_{\text{D}}^{25} -98$  (c 1.11, EtOH; 91% ee). IR (KBr) 3061, 3026, 2886, 1652, 1600, 1494, 1455, 1319, 1291, 1020, 914, 787, 761, 724, 693  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 4.12 (d, 1H,  $J$  = 12.8 Hz), 4.44 (d, 1H,  $J$  = 12.8 Hz), 5.05 (d, 1H,  $J$  = 2.8 Hz), 5.43 (d, 1H,  $J$  = 2.8 Hz), 7.23–7.58 (m, 15H). Anal. Calcd for  $\text{C}_{22}\text{H}_{19}\text{NO}$ : C, 84.34; H, 6.07; N, 4.47%. Found: C, 84.13; H, 6.14; N, 4.48%. The enantioselectivity was determined by HPLC (Daicel Chiralcel OD-H  $\times$  2, hexane/*i*PrOH = 100/1, detected at 254 nm).

**(*S*)-2-Benzyl-3-(2-bromophenyl)-5-phenyl-2,3-dihydroisoxazole (5Ba):** An oil.  $[\alpha]_{\text{D}}^{25} -188$  (c 1.37, EtOH; 93% ee). IR (neat) 3061, 3030, 2924, 2851, 1649, 1600, 1494, 1464, 1022, 752, 725, 694  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 4.18 (d, 1H,  $J$  = 13.2 Hz), 4.41 (d, 1H,  $J$  = 13.2 Hz), 5.44 (d, 1H,  $J$  = 3.0

Hz), 5.54 (d, 1H,  $J = 3.0$  Hz), 7.01-7.54 (m, 13H), 7.73 (d, 1H,  $J = 9.6$  Hz). HRMS (FAB<sup>+</sup>) ( $M + H$ )<sup>+</sup>, Found:  $m/z$  392.06568. Calcd for C<sub>22</sub>H<sub>19</sub>NO<sup>79</sup>Br: 392.06500. The enantioselectivity was determined by HPLC (Daicel Chiralcel OD-H × 2, hexane/<sup>i</sup>PrOH = 200/1, detected at 254 nm).

**(S)-2-Benzyl-3-(4-bromophenyl)-5-phenyl-2,3-dihydroisoxazole (5Ca):** A solid. Mp 63–65 °C (from EtOH).  $[\alpha]_D^{25} -148$  (c 0.62, EtOH; 86% ee). IR (KBr) 3030, 2875, 1653, 1600, 1484, 1071, 1011, 827, 762, 722, 693 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 4.08 (d, 1H,  $J = 12.7$  Hz), 4.44 (d, 1H,  $J = 12.7$  Hz), 5.01 (d, 1H,  $J = 2.8$  Hz), 5.39 (d, 1H,  $J = 2.8$  Hz), 7.01-7.57 (m, 14H). Anal. Calcd for C<sub>22</sub>H<sub>18</sub>NOBr: C, 67.35; H, 4.59; N, 3.57%. Found: C, 67.65; H, 4.69; N, 3.71%. The enantioselectivity was determined by HPLC (Daicel Chiralcel IA × 2, hexane/<sup>i</sup>PrOH = 100/1, detected at 254 nm).

**(S)-2-Benzyl-5-(4-pentylphenyl)-3-phenyl-2,3-dihydroisoxazole (5Ab):** A solid. Mp 60–61 °C (from EtOH).  $[\alpha]_D^{25} -33$  (c 1.70, EtOH; 93% ee). IR (KBr) 3109, 3026, 2914, 2845, 1651, 1509, 1494, 1452, 1415, 1271, 1215, 1073, 1014, 932, 837, 795, 745, 731, 694 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 0.89 (t, 3H,  $J = 6.3$  Hz), 1.23-1.37 (m, 4H), 1.54-1.66 (m, 2H), 2.60 (t, 1H,  $J = 6.7$  Hz), 4.10 (d, 1H,  $J = 12.8$  Hz), 4.43 (d, 1H,  $J = 12.8$  Hz), 5.03 (d, 1H,  $J = 2.8$  Hz), 5.36 (d, 1H,  $J = 2.8$  Hz), 7.15-7.57 (m, 14H). HRMS (FAB<sup>+</sup>) ( $M + H$ )<sup>+</sup>, Found:  $m/z$  384.23322. Calcd for C<sub>27</sub>H<sub>30</sub>NO: 384.23274. The enantioselectivity was determined by HPLC (Daicel Chiralcel OD-H × 2, hexane/<sup>i</sup>PrOH = 80/1, detected at 254 nm).

**(S)-2-Benzyl-5-(4-bromophenyl)-3-phenyl-2,3-dihydroisoxazole (5Ac):** A solid. Mp 115–116 °C (from EtOH).  $[\alpha]_D^{25} -148$  (c 0.62, EtOH; 85% ee). IR (KBr) 3028, 2898, 1651, 1600, 1567, 1494, 1463, 1450, 1317, 1295, 1262, 1249, 1115, 1047, 1026, 970, 948, 860, 767, 747, 723, 690 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 4.08 (d, 1H,  $J = 12.7$  Hz), 4.44 (d, 1H,  $J = 12.7$  Hz), 5.01 (d, 1H,  $J = 12.4$  Hz), 5.39 (d, 1H,  $J = 12.4$  Hz), 7.01-7.57 (m, 14H). Anal. Calcd for C<sub>22</sub>H<sub>18</sub>NOBr: C, 67.35; H, 4.85; N, 3.57%. Found: C, 67.23; H, 4.68; N, 3.54%. The enantioselectivity was determined by HPLC (Daicel Chiralcel OD-H × 2, hexane/<sup>i</sup>PrOH = 100/1, detected at 254 nm).

**(S)-2-Benzyl-5-butyl-3-phenyl-2,3-dihydroisoxazole (5Ad):** An oil.  $[\alpha]_D^{25} -125$  (c 1.02, EtOH; 80% ee). IR (neat) 3062, 3029, 2956, 2929, 2871, 1673, 1602, 1494, 1455, 1305, 1156, 1075, 1029, 955, 732, 697 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 0.92 (t, 3H,  $J = 7.2$  Hz), 1.35-1.44 (m, 2H), 1.51-1.58 (m, 2H), 2.22 (t, 2H,  $J = 8.0$  Hz), 4.01 (d, 1H,  $J = 12.8$  Hz), 4.30 (d, 1H,  $J = 12.8$  Hz), 4.66 (d, 1H,  $J = 1.2$  Hz), 4.85 (d, 1H,  $J = 1.2$  Hz), 7.18-7.43 (m, 10H). HRMS (FAB<sup>+</sup>) ( $M + H$ )<sup>+</sup>, Found:  $m/z$  294.18525. Calcd for C<sub>20</sub>H<sub>24</sub>NO: 294.18579. The enantioselectivity was determined by HPLC (Daicel Chiralcel OD × 2, hexane/<sup>i</sup>PrOH = 100/1, detected at 254 nm).

**(S)-2-Benzyl-5-hexyl-3-phenyl-2,3-dihydroisoxazole (5Ae):** An oil.  $[\alpha]_{\text{D}}^{25} -101$  (c 0.90, EtOH; 85% ee). IR (neat) 3062, 3029, 2953, 2928, 2857, 1673, 1602, 1495, 1455, 1303, 1156, 1074, 1029, 731, 697  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 0.89 (t, 3H,  $J$  = 6.7 Hz), 1.19-1.39 (m, 4H), 1.51-1.63 (m, 4H), 2.21 (t, 2H,  $J$  = 7.6 Hz), 4.01 (d, 1H,  $J$  = 12.8 Hz), 4.30 (d, 1H,  $J$  = 12.8 Hz), 4.66 (d, 1H,  $J$  = 1.2 Hz), 4.85 (d, 1H,  $J$  = 1.2 Hz), 7.18-7.42 (m, 10H). HRMS ( $\text{FAB}^+$ ) ( $\text{M} + \text{H}$ ) $^+$ , Found:  $m/z$  322.21740. Calcd for  $\text{C}_{22}\text{H}_{28}\text{NO}$ : 322.21709. The enantioselectivity was determined by HPLC (Daicel Chiralcel OD-H  $\times$  2, hexane/ $i$ PrOH = 300/1, detected at 254 nm).

**Hydroxymethylation of 4-Isoxazoliny Zinc Intermediate with Formaldehyde (Scheme 1):** To a toluene (3 mL) solution of (*R,R*)-DTBT (26 mg, 0.1 mmol) was added dimethylzinc (0.8 mL of 1.0 M solution in hexane, 0.8 mmol) at 0 °C under an argon atmosphere, and the mixture was stirred for 10 min. To the solution, a toluene (3 mL) solution of racemic *N*-benzyl-*N*-[1-(4-methoxyphenyl)-3-phenylprop-2-ynyl]hydroxylamine (34 mg, 0.1 mmol) was added, and the mixture was stirred for 10 min. A toluene (3 mL) solution of nitron **2A** (106 mg, 0.5 mmol) and a toluene (3 mL) solution of phenylacetylene (**3a**) (51 mg, 0.5 mmol) were added to the resulting solution successively. The reaction mixture was kept for 18 h at 0 °C. Then additional dimethylzinc (1.6 mL of 1.0 M solution in hexane, 1.6 mmol) was further added to the reaction mixture at 0 °C. The resulting solution was warmed up to 25 °C and stirred for 1 d. A freshly prepared THF (5 mL) solution of formaldehyde, produced by thermal decomposition of paraformaldehyde (300 mg), was added to the resulting solution. The reaction mixture was kept at 25 °C for 12 h and quenched by addition of a saturated aq.  $\text{NH}_4\text{Cl}$  solution. After filtration of the precipitate, the filtrate was extracted with AcOEt. The combined extracts were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and condensed under reduced pressure. The residue was separated by TLC on  $\text{SiO}_2$  (hexane/AcOEt = 3/1) to isolate the corresponding alcohol **6** (90 mg, 52%, 85% ee).

**(S)-(2-Benzyl-3,5-diphenyl-2,3-dihydroisoxazol-4-yl)methanol (6):** An oil.  $[\alpha]_{\text{D}}^{25} -1$  (c 0.90, EtOH; 85% ee). IR (neat) 3350, 3062, 3030, 2923, 1685, 1600, 1542, 1492, 1454, 1328, 1272, 1047, 917, 879, 757, 698  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 1.51 (s, 1H), 4.05 (d, 1H,  $J$  = 12.8 Hz), 4.16 (d, 1H,  $J$  = 12.8 Hz), 4.35 (d, 1H,  $J$  = 12.8 Hz), 4.41 (d, 1H,  $J$  = 12.8 Hz), 5.11 (s, 1H), 7.27-7.42 (m, 15H). HRMS ( $\text{FAB}^+$ ) ( $\text{M} + \text{H}$ ) $^+$ , Found:  $m/z$  328.16992. Calcd for  $\text{C}_{23}\text{H}_{22}\text{NO}$ : 328.17014. The enantioselectivity was determined by HPLC (Daicel Chiralcel OD-H  $\times$  2, hexane/EtOH = 10/1, detected at 254 nm).

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6. The absolute stereochemistry of the obtained 4-isoxazolines **5** was determined to be *S*, because the inversion of the stereochemistry was in principle impossible during the cyclization,
7. Partial racemization might have slightly occurred during this step.
8. The precise mechanism of the asymmetric addition reaction to nitrones **2** is still an open question. Especially, the role of the methylzinc salt of a product-like racemic hydroxylamine **4** in the enantiomeric enhancement remains to be accounted for. The easier assembly of the methylzinc salts of a racemic mixture of the product-like hydroxylamines compared with that of the optically pure (*R*)- or (*S*)-product-like hydroxylamine seems to be noteworthy for such the phenomenon.